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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,717	01/08/2002	Yuki Wakabayashi	NITT.0052	8912

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,717	WAKABAYASHI ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status

1. Claims 1-2 are pending.

Claims 1-2 are rejected.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 20, 2006 has been entered.

Claim Rejections - 35 USC § 112

3. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the final detecting step states that the pyrophosphoric acid is detected but then states "wherein the deoxynucleotide solution does not contain DNA primer, the nucleic target acid and the reagent" immediately after a step where these components are added to the deoxynucleotide solution. This renders the claim unclear because there are two different possible interpretations. One interpretation is that the reagents are again removed from the deoxynucleotide solution. However, no basis for this subsequent removal is found in the specification. Another interpretation, which will be

used in the prior art rejections below, is that the phrase simply refers back to the initial deoxynucleotide solution and indicates a property of that solution prior to reaction.

Claim Rejections - 35 USC § 102

4. The rejection of claims 1-4 and 8-9 under 35 U.S.C. 102(b) as being anticipated by Nyren et al (WO 98/13523) are withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The rejections of claims 10 and 13 under 35 U.S.C. 103(a) is moot in view of the cancellation of those claims.

8. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (WO 98/28440) in view of Nyren et al (WO 98/13523).

Nyren et al (WO 98/28440) teaches a *method of analysis of DNA sequence* of claim 1 (see abstract), *comprising the steps of*:

(a) *treating a deoxynucleotide solution containing deoxynucleotides for a complementary strand extension reaction by degrading, using pyrophosphatase, pyrophosphoric acid contained in the deoxynucleotide solution* (see page 19, lines 2-9, where Nyren (WO 98/28440) teaches including a pyrophosphatase in the NTP solutions, where NTP is an alternative term identical in meaning to deoxynucleotide)

(c) mixing the deoxynucleotide solution with reaction solution that contains a DNA primer, a target nucleic acid and a reagent for the extension reaction on the DNA primer after the step of removing or inactivating (see page 30 and example 1, where Nyren et al (WO 98/28440) teaches mixing the deoxynucleotide solution with DNA primers, target nucleic acids and polymerases);

(d) conducting the extension reaction on the DNA primer hybridized to the target nucleic acid, the extension reaction consisting of a plurality of one base extensions wherein the deoxynucleotide solution is aded to the reaction solution per each of said plurality of one base extensions (see example 1 of Nyren (WO 98/28440) at page 33, subheading "DNA sequencing" where Nyren teaches that "The sequencing procedure was carried out by stepwise elongation of the primer strand upon sequential addition of the different deoxynucleoside triphosphates" and

(e) detecting pyrophosphoric acid generated by the extension reaction after the removing or inactivating step wherein the original deoxynucleotide solution did not contain DNA primer, target nucleic acid or reagent (see page 6 and see page 7 for methods of detection using luciferase and example 1 for detection of the extension reaction).

With regard to claim 2, Nyren et al (WO 98/28440) teaches immobilization of the nucleotide degrading enzyme on a solid (see page 6).

Nyren et al (WO 98/28440) recognizes the problem of Ppi contamination in deoxynucleotide solutions (see page 19, lines 2-9) and recognizes that a solution is the addition of pyrophosphatase (see page 19, lines 2-9).

Nyren et al (WO 98/28440) does not teach inactivation or removal of the enzyme in the nucleotide mix.

Nyren et al (WO 98/13523) teaches that ATP may also be a contaminant in reagent solutions and suggests removal of ATP from the reagent solutions (see page 7).

Nyren et al (WO 98/13523) further expressly teaches step *(b) removing or inactivating the enzyme in the deoxynucleotide solution after the pretreating step,* noting that after the contaminant ATP is removed from the reagent solution prior to addition to the reaction mix , "The immobilized enzyme may be removed prior to chain extension/detection (see page 7)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to remove Ppi from the deoxynucleotide solutions prior to addition to the reaction mix since Nyren et al (WO 98/28440) teaches "In carrying out the method of the invention, any possible contamination of the reagents e.g. the NTP solutions, by PPi is undesirable and may readily be avoided by including a pyrophosphatase, preferably in low amounts in the reagent solutions (see page 19, paragraph 1)." Nyren et al (WO 98/28440) recognizes a problem, which is contamination of the deoxynucleotide solutions with Ppi and recognizes that part of the solution is to add pyrophosphatase. Nyren et al (WO 98/28440) does not teach that the enzyme be removed prior to reaction. Nyren et al (WO 98/13523), in addressing the same concern regarding a different contaminant in the same type of pyrosequencing reaction expressly suggests that after the contaminant is removed, the enzyme that acts should itslef be removed, noting ""The immobilized enzyme may be removed prior to chain extension/detection (see page 7)."

Therefore, an ordinary practitioner would have been motivated by each of the Nyren prior art references to use pyrophosphatase Ppi from the deoxynucleotide solution in order improve reaction efficiency and minimize contamination, thereby maximizing real signal. Again, Nyren et al (WO 98/13523) expressly motivates removal of the enzymes prior to addition to the reaction mix, noting "The immobilised enzyme may then be removed prior to the chain extension/detectoin (see page 7, paragraph 2)." This leads to the conclusion that an ordinary practitioner would have been motivated to

remove all the contaminants from the reagent solutions prior to the reacton mixture being formed, and removed the enzymes after treatment, in order to maximize reaction efficiency and minimize contaminating signal.

9. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (WO 98/28440) in view of Rothberg (US 2002/0012930 A1).

Nyren et al (WO 98/28440) teaches a *method of analysis of DNA sequence* of claim 1 (see abstract), *comprising the steps of*:

(a) *treating a deoxynucleotide solution containing deoxynucleotides for a complementary strand extension reaction by degrading, using pyrophosphatase, pyrophosphoric acid contained in the deoxynucleotide solution* (see page 19, lines 2-9, where Nyren (WO 98/28440) teaches including a pyrophosphatase in the NTP solutions, where NTP is an alternative term identical in meaning to deoxynucleotide)

(c) mixing the deoxynucleotide solution with reaction solution that contains a DNA primer, a target nucleic acid and a reagent for the extension reaction on the DNA primer after the step of removing or inactivating (see page 30 and example 1, where Nyren et al (WO 98/28440) teaches mixing the deoxynucleotide solution with DNA primers, target nucleic acids and polymerases);

(d) conducting the extension reaction on the DNA primer hybridized to the target nucleic acid, the extension reaction consisting of a plurality of one base extensions wherein the deoxynucleotide solution is aded to the reaction solution per

each of said plurality of one base extensions (see example 1 of Nyren (WO 98/28440) at page 33, subheading "DNA sequencing" where Nyren teaches that "The sequencing procedure was carried out by stepwise elongation of the primer strand upon sequential addition of the different deoxynucleoside triphosphates" and

(e) detecting pyrophosphoric acid generated by the extension reaction after the removing or inactivating step wherein the original deoxynucleotide solution did not contain DNA primer, target nucleic acid or reagent (see page 6 and see page 7 for methods of detection using luciferase and example 1 for detection of the extension reaction).

With regard to claim 2, Nyren et al (WO 98/28440) teaches immobilization of the nucleotide degrading enzyme on a solid (see page 6).

Nyren et al (WO 98/28440) recognizes the problem of PPi contamination in deoxynucleotide solutions (see page 19, lines 2-9) and recognizes that a solution is the addition of pyrophosphatase (see page 19, lines 2-9).

Nyren et al (WO 98/28440) does not teach inactivation or removal of the enzyme in the nucleotide mix.

Rothberg expressly teaches step *(b) removing or inactivating the enzyme in the deoxynucleotide solution after the pretreating step,* noting "For most applications, it is desirable to use reagents free of contaminants like ATP and PPi. These contaminants may be removed by flowing the reagents through a precolumn containing apyrase

and/or pyrophosphatase bound to resin. Alternatively, the apyrase or pyrophosphatase can be bound to magnetic beads and used to remove contaminating ATP and PPi present in the reagents (see page 11, paragraph 0120)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to remove PPi from the deoxynucleotide solutions prior to addition to the reaction mix since Nyren et al (WO 98/28440) teaches "In carrying out the method of the invention, any possible contamination of the reagents e.g. the NTP solutions, by PPi is undesirable and may readily be avoided by including a pyrophosphatase, preferably in low amounts in the reagent solutions (see page 19, paragraph 1)." Nyren et al (WO 98/28440) recognizes a problem, which is contamination of the deoxynucleotide solutions with Ppi and recognizes that part of the solution is to add pyrophosphatase. Nyren et al (WO 98/28440) does not teach that the enzyme be removed prior to reaction. Rothberg, in addressing the same concern regarding the same contaminant in reagent solutions in the same pyrosequencing reaction expressly suggests that after the contaminant is removed, the enzyme that acts should itslef be removed, noting ""The immobilized enzyme may be removed prior to chain extension/detection (see page 7)."

Therefore, an ordinary practitioner would have been motivated by each of the Nyren prior art references to use pyrophosphatase Ppi from the deoxynucleotide solution in order improve reaction efficiency and minimize contamination, thereby maximizing real signal. Again, Nyren et al (WO 98/13523) expressly motivates removal

of the enzymes prior to addition to the reaction mix, noting "For most applications, it is desirable to use reagents free of contaminants like ATP and PPi. These contaminants may be removed by flowing the reagents through a precolumn containing apyrase and/or pyrophosphatase bound to resin. Alternatively, the apyrase or pyrophosphatase can be bound to magnetic beads and used to remove contaminating ATP and PPi present in the reagents (see page 11, paragraph 0120)." This leads to the conclusion that an ordinary practitioner would have been motivated to remove all the contaminants from the reagent solutions prior to the reacton mixture being formed, and removed the enzymes after treatment, in order to maximize reaction efficiency and minimize contaminating signal.

Response to Arguments

10. Applicant's arguments filed December 22, 2005 have been fully considered but they are not persuasive.

Applicant argues each of the references separately. Because the rejection using the two Nyren references was significantly reworked in view of Applicant's amendment, the argument does not appear applicable to the rejection as written. When Applicant argues that the 102 falls, Applicant is correct. However, the combination of the two Nyren references suggests the invention for the reasons discussed in the rejection.

Applicants arguments do not address the newly made rejection including the Rothberg reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
2/22/06